Perinatal Asphyxia and Thrombocytopenia

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✔ In this study, thrombocytopenia incidence and the mechanism responsible for the thrombocytopenia in asphyxiated infants were investigated within 2 weeks of life. We studied 24 full-term newborn infants with asphyxia and 10 term healthy newborns. Thrombocytopenia developed in 25% of the infants in 0-2 days, 36.8% in 3-6 days and 26.6% in 7-14 days after birth. The mortality ratio in perinatal asphyxia was 29.1% and only one patient had thrombocytopenia. Although the mean platelet volume values of asphyxiated-thrombocytopenic patients were higher than those of the asphyxiated-nonthrombocytopenic patients, no statistical difference was found. We couldn't find any effect of the thrombocytopenia on mortality in perinatal asphyxia. Moreover, the severity of hypoxic ischemic encephalopathy didn't show any relation with platelet count.
Key words: *Newborn, asphyxia, thrombocytopenia*

✔ **Perinatal Asfiksi ve Trombositopeni**
Bu çalışmada asfiktik term yenidoğanlarda hayatın ilk iki haftası içinde trombositopeni insidansı ve trombositopeniden sorumlu mekanizma araştırıldı. 24 asfiksili bebek ve 10 sağlıklı bebek çalışıldı. Asfiktik bebeklerde hayatın ilk iki günü içinde %25.0, 3-6. günlerde %36.8 ve 7-14. günlerde %26.6 oranında trombositopeni gelişti. Perinatal asfiksili infantlarda mortalite oranı %29.1'di ve yalnızca bir hastada trombositopeni vardı. Bu çalışmada perinatal asfikside trombositopeninin mortalite üzerine etkisi bulunamadı. Asfiktik trombositopenik hastaların ortalama trombosit volümü asfiktik nontrombositopenik bebeklerden yüksek olmasına rağmen istatistiksel fark gözlenmedi. Ayrıca hipoksik-iskemik ensefalopati şiddeti trombosit sayısıyla ilişkili değildi.
Anahtar kelimeler: *Yenidoğan, asfiksi, trombositopeni*

INTRODUCTION

Neonatal thrombocytopenia is a common disorder in neonatal intensive care units. Healthy infants have the same platelet counts as adults[1]. The definition of thrombocytopenia in newborns is the same as that in adults: a platelet count of fewer than $150x10^9$per L[2]. It is more common among infants with neonatal asphyxia, respiratory distress syndrome, pulmonary hypertension, or neonatal meconium aspiration. The etiology of this thrombocytopenia is not entirely clear[3,4]. The mean platelet volume (MPV) is a useful test to help categorize thrombocytopenia. Increased platelet size is a marker for "young" or "stressed" platelets, indicating an increased rate of platelet production in response to an increased rate of destruction[5]. Thrombocytopenia may be with serious hemorrhage leading to death or to serious neurologic impairment. Because thrombocytopenia is usually accompanied by comorbid conditions, the clinical impact is more difficult to clarify[6].

In this study, thrombocytopenia incidence and the mechanism responsible for the thrombocytopenia in asphyxiated infants was investigated within 2 weeks of life. Whether the platelet count had any effect on mortality rate in perinatal asphyxia and whether any correlation existed between the severity of hypoxic-ischemic encephalopaty (HIE) and the platelet count were evaluated.

MATERIAL AND METHODS

The study population was consisted of 24 full-term newborn infants with asphxia (group I) and 10 healthy newborns (group II). The following factors were noted in each infant: sex, birth weight, gestational age, and condition at birth including Apgar scores, respiratory status, sepsis, hyperbilirubinemia, medications, clinical course, and outcome. The gestational age of all infants was determined by a combination of maternal dates and Dubowitz score[7]. The infants whose gestational ages were between 38 and 42 weeks were enrolled in the study. All infants' weight was above 2500 g. The newborns whose Apgar score at fifth minute was 5 or below, and arterial blood pH during birth or a few hours after birth below 7.2, and had the findings of HIE were accepted as having perinatal asphyxia. Patients were recorded according to the HIE staging of Sarnat and Sarnat[8]. All mothers were evaluated with respect to age, parity, complications of pregnancy, and medications during pregnancy. The patients with the maternal disorders like bacterial or viral infections, severe hypertension, idiopathic purpura, placental disorders like vascular thrombosis, abrubtio placenta, and those using medications causing thrombocytopenia during pregnancy, and/or the cases with diseases of the newborn such as congenital leukemia, bacterial sepsis, necrotizing enterocolitis and the those having exchange transfusion were all excluded from the study.The blood samples were collected in asphyxiated infants in three different times named as period. The same tests were performed in control infants in two different times after parental consent was obtained. The first period was within 48 hours after birth, the second was between the third and the sixth days after birth, and the third period between the seventh and the fourteenth days after birth. All asphyxiated babies had coagulation work-up including prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrin degradation products to rule out disseminated intravascular coagulation (DIC). Transfontanel and abdominal ultrasonographic examinations were performed to evaluate intracranial hemorrhage and renal vein thrombosis in the asphyxiated newborns. The mechanism responsible for the thrombocytopenia was investigated by measuring MPV. The platelet count and MPV was assessed on EDTA anticoagulated specimens using a coulter-S+ counter (Coulter STKS, Coulter Electronics Ltd Northwell Drive, England). The asphyxiated infants were divided into two groups according to the platelet counts. If platelet count was less than $150x10^9$/L, those were named as thrombocytopenic infants (group Ia) and if more than $150x10^9$/L as nonthrombocytopenic infants (group Ib). Thrombocytopenia, when present, was confirmed by examination of a stained blood film.

The results of parameters in both groups were compared with Mann-Whitney U-test. Wilcoxon Matched-Pairs Signed-Ranks test was used to find the difference of the parameters among periods. Platelet count and severity of HIE were compared with Kruskal-Wallis one-way-anova test.

RESULTS

Asphyxiated and control groups were not different for matched features, which included birth weight and gestational age. However, a major difference between the two groups was the Apgar score.

Table I shows the value of platelet count and MPV of groups in different periods. Thrombocytopenia ratio in the asphyxiated patients was 25.0% in the first period, 36.8% in the second period and 26.6% in the third period. Thrombocytopenia were determined in 9 patients during the first two weeks of life. Thrombocytopenia didn't occur in the healthy cases. There was no statistical difference between the platelet counts and MPV values of patient and control groups. Although MPV values of asphyxiated-thrombocytpopenic patients were higher than those of the asphyxiated-nonthrombocytpopenic patients, no statistical difference was found.

Seven patients died during the study (mortality ratio 29.1%). Five patients died on the third day, two patients on the eleventh day after birth. Only one patient had thrombocytopenia. All the patients who died had stage III HIE findings. We couldn't find any effect of the thrombocytopenia in perinatal asphyxia on mortality (Table II).

Table I. Platelet Counts and The Mean Platelet Volumes of The Groups in Different Periods.

		Group I	Group II	Group Ia	Group Ib
Period I	Plt	181.67±13.56	179.30±10.02	138.33±24.62*	207.67±12.12*
	MPV	8.24±0.16	8.69±0.15	8.66±0.30	7.99±0.16
Period II	Plt	184.39±22.48		103.75±20.12**	248.90±20.62**
	MPV	8.73±0.22	215.10±10.38	9.09±0.25	8.44±0.33
Period III	Plt	258.27±42.30	8.86±0.14	191.13±52.98	335.00±58.02
	MPV	8.67±0.22		8.91±0.49	8.40±0.56

Values are given in mean±SE.

*: $p < 0.05$ **: $p < 0.01$

Table II. The Follow-up Results of the Patients with or without Thrombocytopenia in Different Periods.

Periods			0-2 days		3-6 days		7-14 days	
No of patients		with thrombocytopenia	6		7		4	
		without thrombocytopenia	18		12		11	
	Alive		19		15*		13	
Outcome	Exitus	with thrombocytopenia	5	1	–	–	2	–
		without thrombocytopenia		4		–		2

* Four patients of 19 were discharged

There were 12 patients in stage I, 3 patients in stage II and 9 patients in stage III according to HIE staging. Of the 9 thrombocytopenic infants, 4 had stage I, 2 had stage II, and 3 had stage III HIE findings. We couldn't find any relation between the severity of HIE and platelet count (Table III).

Table III. Platelet Counts in Different Periods due to Stages of HIE.

Stages of HIE	Group I		
	0-2 days	3-6 days	7-14 days
Stage I	198.16±19.72	173.09±32.20	232.37±54.22
Stage II	153.00±22.81	135.66±31.54	230.33±110.42
Stage III	168.11±23.54	202.00±56.67	331.00±95.36

Values are given in mean±SE.

DIC was diagnosed in the presence of a prolonged PT, PTT and elevated fibrinogen-fibrin degradation products. No DIC developed in any of the patients. Renal vein thrombosis and intracranial hemorrhage were not detected in any of the patients.

DISCUSSION

Thrombocytopenia is very frequent among ill newborns, occurring in 20 to 30% of all admissions to a neonatal intensive care unit. It may be accompanied by serious hemorrhage leading to death or to serious neurologic impairment[2,4,9]. Thrombocytopenia can be caused by decreased platelet production, increased platelet destruction, platelet pooling in an enlarged spleen, or a combination of these mechanisms[8]. It can complicate the clinical course in the sick infant. There is little information regarding the frequency, natural history, or mechanisms responsible for the thrombocytopenia. Some investigators suggest that decreased platelet production is present; others report that increased platelet destruction is the primary mechanism[9]. Increased platelet size is a marker for "young" or "stressed" platelets, indicating an increased rate of platelet production in response to an increased rate of destruction [5]. MPV of newborn platelets is similar to that of the adult, with values usually less than 10 fL and averaging between 7 and 9fL[1,10]. In thrombocytopenic infants MPV increases significantly by day 7 of life. Sick nonthrombocytopenic infants also increase their MPV by day 7 and have a fall in their platelet counts, suggesting that increased consumption of platelets occurs in many sick infants[8].

In one study, no specific etiology of the thrombocytopenia could be incriminated in 60% of the neonatal thrombocytopenias. However, over 50% of babies with depressed platelet counts had umbilical line placement, hypoxia, respiratory assistance, hyperbilirubinemia, and/or phototherapy[11]. Castle and collegues[9] have shown that transient, destructive thrombocytopenia develops in a large proportion (22%) of infants admitted to a neonatal intensive care unit, and that birth asphyxia is an important risk factor. The platelet count nadir usually occurred by day 4 and resolved within 2 weeks of life.

Birth asphyxia has consistently been associated with evidence of DIC and thrombocytopenia in sick infants. The clinical

observation is supported by animal studies that directly link exposure to hypoxia with thrombocytopenia[8]. The effect on platelet counts in animals was found to be related to the duration of hypoxemia[12]. In one study, an hypoxic insult in mice maintained for period of 1 to 3 days has resulted in an initial increase in platelet numbers followed by thrombocytopenia[13]. In another study it has been shown that acute, severe hypoxia, one component of birth asphyxia (without acidemia), significantly shortens the platelet survival time[14]. Hypoxia has been found in laboratory rats to depress platelet production by altering megakaryocyte structural and functional characteristics[15].

In the previous studies contribution of perinatal asphyxia on the development of thrombocytopenia has been pointed out but thrombocytopenia ratio and direct effect of the thrombocytopenia on mortality in perinatal asphyxia has not been reported. Moreover, the etiology of this thrombocytopenia is not entirely clear. We found a 37.5% of thrombocytopenia incidence during the first two weeks. The ratios were 25.0%, 36.8% and 26.6% during 0-2 days, 3-6 days and 7-14 days, respectively. The mechanism responsible for the thrombocytopenia was investigated by measuring MPV. Although MPV values of asphyxiated-thrombocytopenic patients were higher than those of the asphyxiated-nonthrombocytopenic patients, no statistical difference was found. The higher value of MPV in the second period in which thrombocytopenia is frequent may suggest that the thrombocytopenia in the asphyxia is due to increased platelet destruction. Seven patients died during the course of study (mortality ratio 29.1%). All the patients who died had stage III HIE findings. Only one patient had thrombocytopenia. We couldn't find any effect of the thrombocytopenia on mortality ratio in perinatal asphyxia.

There is no study about the effect of the severity of HIE on platelet count. We couldn't also find any correlation between the severity of HIE and platelet count. Further investigations studying larger populations of perinatal asphyxiated newborns are needed to confirm our results.

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